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TITLE: **Improving PTSD Outcomes in OIF/OEF Returnees: A Randomized Clinical Trial of Hydrocortisone Augmentation of Prolonged Exposure Therapy**

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14. ABSTRACT

Purpose: To examine longitudinally, biological and psychological alterations in veterans with PTSD. Scope: To obtain a range of symptom severity over time, we will manipulate symptoms using two conditions: Prolonged Exposure (PE), and Minimal Attention (MA). The study will address the extent to which factors hypothesized to be associated with risk, symptom severity, and recovery have differing correlates by examining several biological and psychological variables in veterans who do and do not show recovery in response to PE, an intervention that alleviates PTSD symptoms in many subjects, compared to those in an MA condition. Epigenetic mechanisms associated with PTSD risk and recovery will also be considered.
Major Findings: IC50 as predictor of treatment response, Methylation of the GR as predictor of clinical status

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Annual Report for Army Award W81XWH-10-2-0072

Title: 'Improving PTSD Outcomes in OIF/OEF Returnees: A Randomized Clinical Trial of Hydrocortisone Augmentation of Prolonged Exposure Therapy'

PI: Rachel Yehuda, PhD

Submitted 8.23.12

Study Site Information: The study takes place entirely at the James J. Peters VAMC, and within the Traumatic Stress Studies Division at that site. Prospective and enrolled participants are interviewed in the clinical research space adjacent to the PTSD Clinic. Dr. Yehuda is the Mental Health Patient Care Center Director (PCCD), Dr. Bierer is the Medical Director of this study and Dr. Golier is the Chief of Psychiatry. Dr. Flory is Manager of the PTSD Clinic. The clinical and research activities of Drs. Bierer and Flory are centered in the PTSD Clinic and Traumatic Stress Studies Division which is directed by Dr. Yehuda.

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I. INTRODUCTION

This study proposes a placebo-controlled pharmacological augmentation of prolonged exposure (PE) therapy provided to OIF/OEF for the treatment of PTSD. The strategy involves the oral administration of the synthetic glucocorticoid, hydrocortisone (Cortef) or placebo prior to the last 8 of 10 treatment sessions. The rationale for this is based on animal studies demonstrating beneficial effects of glucocorticoids (GCs) on aspects of learning relevant to hypothesized mechanisms involved in PE, and on recent clinical findings demonstrating positive effects of GCs on learning, and in reducing traumatic memories in trauma-exposed persons. That PE does not appear to be as effective in the treatment of combat-associated PTSD as in civilian samples further underscores the importance of developing strategies to improve outcome of this treatment among veterans with PTSD. Further, combat veterans demonstrate substantial cognitive alterations, which may or may not be associated with PTSD that may contribute to functional disability, and may affect treatment response. This adds to the relevance of testing the effects of GC administration on PTSD treatment, as evidence suggests that exogenous GCs may improve working memory among veterans.

The primary aim is to determine the effectiveness of Hcort as an augmentation for PE on PTSD symptoms throughout the course of treatment and at follow-up. If pre-session hydrocortisone enhances the effects of treatment, this will identify an important therapeutic strategy for combat veterans. We aim to assess the effects of PE on related clinical and functional measures and on cognitive performance. We aim to correlate the effect of each treatment on PTSD symptoms and cognition to determine whether their alterations are linked. We aim to determine whether biological measures change over treatment, and whether these changes are associated with outcome in the absence or presence of GC augmentation.

Supplemental funding for additional biomarkers

In the last year the aims of the original DOD Hcort/placebo treatment study were enlarged in association with the receipt of plus-up funds to expand the neuroendocrine markers of the initial proposal to include a panel of biomarkers chosen to be identical to several of those obtained n a collaborative cross-sectional study of OIF/OEF returnees entitled 'Biomarkers in PTSD' (PI: Charles Marmar MD; Co-PI: Rachel Yehuda, PhD, and others). Evaluation of biomarkers in the context of a treatment study permits an assessment of the extent to which each (or a subset) may predict or be associated with treatment response. Evaluation of biomarkers in relation to the current treatment study additionally permits assessment of whether any of the chosen biomarkers are differentially affected by the intermittent administration of hydrocortisone prior to treatment sessions in which imaginal exposure takes place. As it was important that the additional biological assessments be incorporated into the current treatment protocol as early as possible, initial funding

for this work was provided as a 'plus-up' supplement to the treatment study. For the next two years, however, supplemental funds will be provided as a separate grant with a distinct project number. The novel measures explore molecular, cellular, immune, and neurochemical indices. Specific measures include genotyping and gene expression studies of the glucocorticoid receptor (by Yehuda/Buxbaum at MSSM); evaluation of cellular metabolic indices in collaboration with Owen Wolkowitz, MD and colleagues at UCSF; telomere length and lymphocyte telomerase activity in collaboration with Elizabeth H. Blackburn, PhD; metabolomics and proteomics with Marti Jett and Lee hood (no funding was requested for the latter studies)[1]; cytokines, and additional neurochemical (BDNF and endocannabinoids) and steroid indices (urinary glucocorticoid metabolites assessed by CGMS, and enzyme indices). An inclusive list of specific supplemental biological measures is provided in ***Table 1*** **(*Appendix*)** and described in Task 4 of the Statement of Work (below).

[1] We did not request funds for a collaboration with M. Jett and L. Hood to investigate metabolomics and proteomics. Rather, an understanding has been achieved such that 'discoverable' biomarkers from Dr. Marmar's study (Biology of PTSD) will be included in this treatment study and evaluated longitudinally.

II. BODY

1. Description of the research accomplishments associated with each task outlined in the approved Statement of Work.

A. Original Statement of Work (annotated with changes to procedures):

Task 1. Obtain necessary authorizations prior to initiation of human subjects' research (0-4 months)

- Obtain final IRB approval for protocol and advertisements. **(*accomplished*)**
- Finalize agreements with JJP VAMC pharmacy and laboratory departments**. (*accomplished*)**
- Complete hiring of necessary staff, and ensure that all required IRB and research trainings are complete. **(*accomplished*)**

Task 2. Initial launch of clinical trial of Prolonged Exposure (PE) with glucocorticoid augmentation (with 30 mg Cortef) or placebo. (0 to 4 months)

- Train new study personnel in the psychological and neuropsychological evaluations. **(*accomplished*)**
- Train and supervise new study personnel in methods of prolonged exposure. **(*accomplished*)**
- Obtain Cortef and placebo from Pfizer, Inc and complete research pharmacy study initiation process. **(*accomplished*)**
  [Hydrocortisone (Cortef) and placebo are obtained from the VA pharmacy, and are prepared for distribution by our Research Pharmacist. Hcort or placebo is distributed to the research coordinators (who administer the drugs prior to each imaginal treatment session) in protective packaging so that neither the research coordinator or participant are aware of the contents (i.e., Hcort or placebo).]
- Create randomization log for stratified recruitment; review blinding and randomization with pharmacy. **(*accomplished*)**
- Create regulatory binders, case report forms and database template; establish data input procedures. **(*accomplished*)**
- Mobilize existing resources within the JJP VAMC so as to identify potentially eligible OIF/OEF veterans, and within the PTSD clinic to identify potential subjects at intake and at later phases of treatment. **(*accomplished*)**
- Develop coordinated referral network within Mental Health and Primary Care at the JJP VAMC and VISN. **(*in progress*)**
- Institute research staff meetings, diagnostic meetings, and supervision schedules. **(*in progress*)**
- Schedule first of four yearly meetings with all investigators to occur at 6, 18, 30, 42 months. ***(accomplished)***
  [The PI and Co-Investigators meet regularly to discuss this protocol.]

Task 3. Screening and Assessment of veterans with PTSD (5 months – 36 months)

- Obtain fully informed consent from potentially eligible veterans. **(*in progress*)**
- Perform comprehensively psychological and medical assessment to determine eligibility for inclusion. ***(in progress)***
- Determine medical and clinical eligibility. If eligible, randomize subject, and schedule for evaluation. ***(in progress)***

Task 4. Initial Evaluation (5 months – 39 months)

- Obtain diagnostic interview, including CAPS, and self-reports of clinical, psychological and functional outcomes. ***(in progress)***

- Obtain initial neuroendocrine biomarkers (verify compliance with procedures); and cognitive assessment. ***(in progress)***
  [Both the cognitive assessment and the list of biomarkers have been changed since the initial submission. The CVLT has been eliminated from the assessment of cognitive performance, and we have added the MATRICS Consensus Cognitive Battery (MCCB). The seven domains of cognitive function that will be assessed are detailed in Table 2, Appendix. As described above, we have expanded the battery of biological markers from that proposed in the original protocol. A sample of molecular, cellular, metabolic, immune, and neurochemical measures associated with stress and aging have been added to the assessment measures. Initial funding for these assessments was in the form of a 'Plus-Up' funds provided as a Supplement to the current protocol last year. For the next two years, however, funding for the additional markers will be received under a separate award. In Table 1 (Appendix), we have listed the original neuroendocrine measures, as well as the additional biomarkers, and the laboratories proposed to execute the respective assays. Thus, the task of measuring biomarkers and of assessing cognitive performance has not changed; we have, however, altered the specific cognitive measures assessed, and have expanded the list of biomarkers beyond the neuroendocrine measures originally proposed .]

- Score, verify, enter data within two months of evaluation – establish procedures for verification of data entry. ***(in progress)***

- Initiate review process of audiotapes for reliability of diagnostic assessment with Dr. Janine Flory**.** ***(in progress)***
  [Dr. Flory directs a consensus conference on a weekly basis during which MINI diagnoses are confirmed and reliability is established for MINI diagnoses and CAPS ratings. Reliability of the assessment procedure is determined on an ongoing basis, and corrective education provided. As audiotapes of diagnostic assessments are not consistently reviewed, the words 'of audiotapes' have been removed from the revised Statement of Work.]

Task 5. Begin treatment (5 months – 39 months)

- Provide 10 sessions of PE with administration of Cortef or placebo 45 min before these sessions. ***(in progress)***
  [We have changed the number of sessions from 10 to 11. There was much to accomplish in Session 2, which resulted in unduly prolonged session meetings. Through-out the VA, Session 2 has been divided into two sessions, 2a and 2b. In accordance, we have changed the procedures for this study. Additionally we now administer hydrocortisone 30mg or placebo 20 minutes prior to each treatment session rather than 45 minutes prior to the sessions. As hydrocortisone is well absorbed, this change was made to better associate the anticipated peak blood level with the imaginal exposure procedure. Finally, as there is substantial inter-individual variation in the diurnal secretion and basal levels of cortisol, and since treatment sessions occur at various times of day, we have instituted a collection of salivary cortisol prior to each pre-session medication ingestion. This pre-session cortisol determination

will permit us to covary for the basal cortisol value in the assessment and interpretation of clinical response to Hcort vs. placebo augmentation of PE therapy. Lastly, the word 'Cortef' has been changed to hydrocortisone in the revised Statement of Work.]

- Obtain CAPS prior to sessions 2, 4, 6, and 8 of PE treatment (in addition to those obtained at the time of evaluations (i.e., at pre-treatment, post-treatment and follow-up). ***(in progress)***
  [We have changed this procedure. Instead of obtaining repeated CAPS - which may be lengthy and associated with excessive subject burden when scheduled immediately prior to an imaginal exposure treatment session-- , we now administer self reports for PTSD (the PDS), depression (Beck Depression Inventory, BDI), and anxiety (Spielberger State-Trait Anxiety Interview – State version) prior to Sessions 2a, 4, 6, and 8. We have recently submitted (6.22.12) an amendment to request completion of these self-reports prior to every treatment session, i.e., Sessions 1, 2a, 2b, 3--10.]

- Monitor for side effects and adverse events. ***(in progress)***
  [There have been no untoward side effects or adverse reactions observed to date.]

- Establish ongoing supervision of cases and procedures to monitor treatment fidelity with Dr. Goodman. ***(task modified)***
  [We have changed this procedure due to the diminished time availability of Dr Goodman, as well as a reflection of the increased competence and familiarity with PE of the participating providers (explained below). Since Dr. Goodman's received a DOD grant to compare DBT with treatment-as-usual for suicidality, she no longer has the time to perform fidelity ratings for this study. (She has agreed, however, to serve as the Research Monitor for the protocol.)

  <u>Background with respect to the basic competence in PE of the providers in this study</u>: Three of the therapists who perform PE as part of this research study have been certified by the VA to perform prolonged exposure. This 'certification' was instituted in association with the nation-wide 'roll-out' of PE as a mandated treatment offering for PTSD in the VA. Two therapists were asked (but declined) to serve as PE supervisors on a national level. Further, within our research team, a rigorous process of training and review is required before a therapist is permitted to provide research-associated prolonged exposure. For this internal 'certification,' the complete audiotapes of the entire treatment of two recipients of non-research-related PE are reviewed by a VA certified, and research qualified psychologist. The patients whose treatment is thus reviewed for training purposes would otherwise have been appropriate for the current protocol (or for the treatment studies described above) – but perhaps would not have been included for medical reasons, etc. In addition to audiotape review, the training psychologist provides weekly supervision to the PE provider. Only after completion of this review and supervision, and a determination that the psychologist in training/under review is capable of providing PE in a strictly adherent manner, is a therapist permitted to provide PE within a treatment study. Thus, the level of competence among our PE providers is considerable, and it is relatively `unlikely that audiotape review will uncover clinically impactful deviations from the manualized optimal technique.

  We have adopted the following procedure for assessing treatment fidelity. As each of the providers participating in this study is qualified to perform fidelity monitoring, we will ask each PE 'certified' provider to rate two of his/her colleagues. Two audiotapes from sessions 3-6 and two from sessions 7-10 will be rated per therapist; the sessions need not be from the same participant(s). A PE session rating form will be used. Melissa D. Altman, PhD will ensure that the ratings are accomplished in a reasonable time frame, and make the results available to the PI and co-Investigators on the project. This procedure is in keeping with the recommendations and procedures used by Paula P. Schnurr, PhD, an expert in the provision and assessment of manualized therapies.[1,2] Details of a plan to accomplish the fidelity ratings were not articulated in the original protocol. We believe the above procedures, with the DOD's approval, will serve to ensure that the treatments provided in this study are faithful to the intent and practice of manualized PE.

[1] Schnurr PP. The rocks and hard places in psychotherapy outcome research. J Trauma Stress. 2007; 20(5):779-92.

[2] Schnurr PP, Friedman MJ, Engel CC, Foa EB, Shea MT, Chow BK, Resick PA, Thurston V, Orsillo SM, Haug R, Turner C, Bernardy N. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. JAMA. 2007; 297(8):820-30.

Task 6: Perform comprehensive evaluations at post-treatment and at follow-up (8 months – 44 months)

- Reassess PTSD symptoms, cognitive performance; obtain self-reports of psychological and functional outcomes. ***(in progress)***

- Obtain repeat neuroendocrine biomarkers (verify compliance with procedures). ***(in progress)***

- Monitor for adverse effects, changes in laboratory values. ***(in progress)***

B. Updated Statement of Work - inclusive of the changes noted above (changes underlined):

Task 1. Obtain necessary authorizations prior to initiation of human subjects' research (0-4 months)

- Obtain final IRB approval for protocol and advertisements. **(*accomplished*)**
- Finalize agreements with JJP VAMC pharmacy and laboratory departments**. (*accomplished*)**
- Complete hiring of necessary staff, and ensure that all required IRB and research trainings are complete. **(*accomplished*)**

Task 2. Initial launch of clinical trial of Prolonged Exposure (PE) with glucocorticoid augmentation (with 30 mg Cortef) or placebo. (0 to 4 months)

- Train new study personnel in the psychological and neuropsychological evaluations. **(*accomplished*)**
- Train and supervise new study personnel in methods of prolonged exposure. **(*accomplished*)**
- Obtain hydrocortisone and placebo from the JJP VAMC research pharmacy and complete research pharmacy study initiation process. **(*accomplished*)**
- Create randomization log for stratified recruitment; review blinding and randomization with pharmacy. **(*accomplished*)**
- Create regulatory binders, case report forms and database template; establish data input procedures. **(*accomplished*)**
- Mobilize existing resources within the JJP VAMC so as to identify potentially eligible OIF/OEF veterans, and within the PTSD clinic to identify potential subjects at intake and at later phases of treatment. **(*accomplished*)**
- Develop coordinated referral network within Mental Health and Primary Care at the JJP VAMC and VISN. **(*in progress*)**
- Institute research staff meetings, diagnostic meetings, and supervision schedules. **(*in progress*)**
- Schedule first of four yearly meetings with all investigators to occur at 6, 18, 30, 42 months. **(*in progress*)**

Task 3. Screening and Assessment Program for veterans with PTSD (5 months – 36 months)

- Obtain fully informed consent from potentially eligible veterans. **(*in progress*)**
- Perform comprehensively psychological and medical assessment to determine eligibility for inclusion. ***(in progress)***
- Determine medical and clinical eligibility. If eligible, randomize subject, and schedule for evaluation. ***(in progress)***

Task 4. Initial Evaluation (5 months – 39 months)

- Obtain diagnostic interview, including CAPS, and self-reports of clinical, psychological and functional outcomes. ***(in progress)***
- Obtain initial neuroendocrine and additional biomarkers (verify compliance with procedures); and cognitive assessment. ***(in progress)***
- Score, verify, enter data within two months of evaluation – establish procedures for verification of data entry. ***(in progress)***
- Initiate review process for reliability of diagnostic assessment with Dr. Janine Flory**. *(in progress)***

Task 5. Begin treatment (5 months – 39 months)

- Provide 11 sessions of PE with administration of hydrocortisone or placebo 20 min before Sessions 3 - 11. ***(in progress)***
- Obtain self reports prior to all sessions of PE treatment (in addition to those obtained at the time of evaluations (i.e., at pre-treatment, post-treatment and follow-up). ***(in progress)***
- Monitor for side effects and adverse events. ***(in progress)***

- Provide training and supervisions to criterion for all providers of PE therapy. ***(complete for all participating psychologist treatment providers)***

Task 6: Perform comprehensive evaluations at post-treatment and at follow-up (8 months – 44 months)

- Reassess PTSD symptoms, cognitive performance; obtain self-reports of psychological and functional outcomes. ***(in progress)***
- Obtain repeat neuroendocrine biomarkers (verify compliance with procedures). ***(in progress)***
- Monitor for adverse effects, changes in laboratory values. ***(in progress)***

2. Subject enrollment update

a. Total projected number of subject enrollment

To accomplish the objectives 80 OIF/OEF must be randomized (with 40 in each of the two groups). Of the 80 randomized, we anticipate 60 will complete all study procedures. This necessitates evaluating 100 study participants and screening 125 subjects.

b. Number of subjects enrolled to date

Table 3 (***Appendix)*** provides a schematic of subject flow, which is described in greater detail below.

Consent and pre-treatment diagnostic evaluation for eligibility: To date, 20 veterans have been consented for the study, 18 of whom were consented since the last annual report was submitted. Of the 20 consenters, 3 discontinued their participation in the study prior to completing any study procedures and 3 currently await initiation of the medical and psychological pre-treatment evaluation. 14 have completed the medical and psychological evaluation for the study. Of these 14, 12 participants were deemed eligible for the study and 2 were determined to be ineligible. Specifically, 1 participant was considered medically ineligible due to laboratory indications of new onset diabetes - and was instead referred to a similar treatment study for which he would be eligible. The other 1 participant was deemed ineligible following the psychological evaluation due to an insufficient CAPS score of 51 - and was also referred to another similar treatment study with a lower pre-treatment CAPS threshold, which he completed.

Pre-treatment research evaluation and treatment participation: Of the 12 participants deemed eligible for the study to date, 11 have completed all pre-treatment evaluation study procedures, which include the completion of self reports, cognitive testing, 24-hour urine, a diurnal saliva collection, and two blood draws (DST day 1 and DST day 2). 1 of the 12 participants is waiting to complete the pre-treatment evaluation as he expressed a desire to be treated by the psychologist assigned to his case who will be on maternity leave until early September, 2012. In total, 11 participants have been randomized. Of these 11, 5 have completed treatment4 are currently in treatment, and 2 dropped out after treatment initiation (1 after PE session #1, and 1 after PE session #5). The first participant suffered a leg injury and was distracted by physical therapy appointments, while the second in the midst of divorce proceedings, and found concurrent PE therapy too stressful.

Post-treatment and follow-up evaluations: Of the 5 participants who completed treatment, all 5 have additionally completed their post-treatment evaluation, which includes a clinician rated psychological evaluation for post-treatment diagnosis (using the MINI), a PTSD assessment (CAPS), self reports, cognitive testing, 24-hour urine, diurnal saliva collection, and two blood draws (DST day 1 and DST day 2). The 3-month follow-up evaluation is identical to that performed at pre- and post-treatment. At this time, all 5 participants who completed their post-treatment evaluation have also completed all follow-up evaluation procedures.

Summary: In total, 20 participants have been consented, 11 have completed pre-treatment evaluations and been randomized, 5 have finished post-treatment and follow-up evaluations.

c. A description of barriers that are hindering subject enrollment efforts

HRPO approval to begin this study was provided on March 28, 2010. The first subject signed consent on 4.28.11. It took until 11/09 for the first set of procedural amendments to be approved at the JJP VAMC and at the MSSM. In addition, there was competition for recruitment into this treatment protocol during the first year or more of funding. Our first effort to test the idea of hydrocortisone (Hcort) augmentation of PE therapy took the form of a small protocol, supported by the MIRECC. A case report of two treatment completers from this initial study was published in Yehuda et al.2010.[1] Following our experience with this small pilot, and using the MIRECC supported protocol as preliminary data for a subsequent grant, we rewrote the study as a somewhat larger but still preliminary treatment protocol, which was funded by the Lightfighter Trust. This preliminary protocol proposed to study 30 veterans with PTSD (completers), and was originally designed to recruit only OIF/OEF subjects. After receiving funding for the current protocol, however, it became apparent that we had two very similar studies which purported to recruit the identical sample. Our IRB requested that we address this overlap. We submitted and were approved for several amendments aimed to differentiate the two studies. The most significant of these was a change in the Lightfighter Trust protocol which opened the study to veterans of any military conflict. Several procedural amendments, enumerated above (in the annotations to the original Statement of Work), to the DOD Hcort study (our moniker for the current protocol) served to further distinguish the studies as well. The Lightfighter Trust protocol is still ongoing, but in the last weeks of funding.

[1]**Yehuda R**, Bierer LM, Pratchett L, Malowney M. Glucocorticoid augmentation of prolonged exposure therapy: rationale and case report. *European Journal of Traumatology.* 2010(1): 5643.

d. Solutions to overcome difficulties with subject enrollment

In the last few months, our original DOD funded PE study comparing PE treatment to an inactive 'Minimal Attention' condition -- has terminated recruitment. This further reduces competition for enrollment into research related PE treatment protocols in the PTSD Clinic. At the present time, our strategy is to enroll into the Lightfighter Trust study only OIF/OEF veterans who would not meet criteria for the current DOD funded Hcort/placebo treatment study.

An important research development serves to enhance recruitment into the DOD funded Hcort/placebo treatment study. The DOD 'Biomarkers in PTSD' study (PI: C. Marmar, MD; Co-PI R. Yehuda, PhD, among others) actively recruits through advertisements OIF/OEF veterans with and without PTSD. This is a cross-sectional study which includes a diagnostic assessment, administration of the CAPS, completion of several self-reports, and cognitive assessment. An MRI performed at NYU is an additional procedure. Veterans, often new to the JJP VAMC, who are evaluated as part of the Biomarkers in PTSD study, and who express a desire for treatment, are introduced to the possibility of participation in the DOD Hcort study.

It is a consequence of the interest developed in biomarkers as a result of the latter multi-center protocol that we have received additional funding to augment the original neuroendocrine battery for the DOD Hcort study with additional biomarkers. By collecting the expanded biomarker panel in association with the current treatment study (***see Table 1***), we will be able to explore which, if any,

of the PTSD associated molecular, cellular, inflammatory and neurochemical markers might predict or be associated with positive treatment response to PE. This will as well provide an invaluable additional dimension to the data derived from the DOD funded 'Biomarkers in PTSD' study.

III. KEY RESEARCH ACCOMPLISHMENTS

Table 4 (***Appendix***) summarizes the research procedures accomplished to date. As stated above, three subjects discontinued participation prior to completing any research procedures, so no data is available for them. Of the 14 participants who completed a pre-treatment psychological evaluation, only 12 met inclusion criteria. Consequently descriptive data is presented for these 12 only.

Table 5 (***Appendix)*** presents the descriptive results of psychological assessments, self-reports, and neuroendocrine data that is currently available for all subjects (i.e., whether they received Hcort or placebo during treatment). Thus, complete psychological and biological data is shown for 12 included subjects at pre-treatment and either 4 or 5 subjects at post-treatment and follow-up evaluations, depending on the number of neuroendocrine assay results available to date. Review of the CAPS data presented in Table 5 suggests that avoidance continues to improve between post-treatment and follow-up evaluations, without consideration of the treatment arm of study (i.e., without consideration of the Hcort/ placebo conditions). This is also seen in self-ratings of avoidance (PSS-SR avoidance subscale), but the trend is less pronounced. A similar trend is descriptively apparent for decrement in the Post-Trauma Cognitions Inventory ratings for 'Negative –Self.'

For the neuroendocrine assessments, there appear to be increases in DHEA and DHEAS between the post-treatment and follow-up evaluations. A different pattern is suggested for glucocorticoid indices, where the treatment associated change may appear between the pre- and post-treatment evaluations. Specifically, the latter pattern is apparent for lymphocyte lysozyme $IC_{50\text{-}DEX}$, percent suppression of cortisol, and the pre- to post-Dex change in plasma cortisol. Clearly with only 5 treatment completers in this sample, even descriptive inferences from these data will likely change as the study progresses. It would be interesting if one of the findings of this investigation was that treatment associated glucocorticoid alterations prefigured consolidation of behavioral gains resulting from treatment, which continued to consolidate over several weeks following treatment termination.

Importantly, the 'data' shown in Table 5 is presented primarily to illustrate that we are performing all steps required to meet the aims of the study, and can manipulate the data to create the outcome variables listed in the protocol. We have not presented the results of the cognitive assessments, but the raw data is available from which specific measures of performance will be derived. Additionally, as we routinely batch assays, glucocorticoid receptor binding has not yet been measured.

IV. REPORTABLE OUTCOMES

There are no reportable outcomes to date.

V. CONCLUSION

Although the current study suffered a substantial delay in its initiation, we are now fully operational. The 'Biomarkers for PTSD' study not only provides a steady stream of newly recruited veterans into research within our Clinic, but is now synergistically positioned scientifically as well. The addition of molecular, cellular, inflammatory, and neurochemical biomarkers -- the majority of those assessed in the 'Biomarkers for PTSD' study – will augment the applicability and importance of the current treatment study immeasurably. We are grateful to the DOD for this opportunity.

VI. REFERENCES

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VII. APPENDICES (see appendix)

Table 1. MATRICS Consensus Cognitive Battery (MCCB): Seven cognitive domains and specific tests for each
Table 2. Original neuroendocrine and supplemental biomarkers integrated into the biological assessment
Table 3. Summary of participant flow to date
Table 4. Research procedures accomplished to date
Table 5. Psychological and neuroendocrine descriptive data to date.

VIII. ADDENDUM

None.

Table 1. MATRICS Consensus Cognitive Battery (MCCB): Seven cognitive domains and specific tests for each.

Cognitive Domain	Test	Description
Speed of processing	*Brief Assessment of Cognition in Schizophrenia* (BACS): Symbol-Coding	Timed paper-and-pencil test in which respondent uses a key to write digits that correspond to nonsense symbols
	Category Fluency: Animal Naming	Oral test in which respondent names as many animals as she/he can in 1 minute
	Trail Making Test: Part A	Timed paper-and-pencil test in which respondent draws a line to connect consecutively numbered circles placed irregularly on a sheet of paper
Attention/Vigilance	*Continuous Performance Test*—Identical Pairs (CPT-IP)*	Computer-administered measure of sustained attention in which respondent presses a response button to consecutive matching numbers
Working memory (nonverbal)	*Wechsler Memory Scale*®—3rd Ed. (WMS®-III): Spatial Span	Using a board on which 10 cubes are irregularly spaced, respondent taps cubes in same (or reverse) sequence as test administrator
(verbal)	*Letter-Number Span*	Orally administered test in which respondent mentally reorders strings of number and letters and repeats them to administrator
Verbal learning	*Hopkins Verbal Learning Test—Revised*™ (HVLT-R™)	Orally administered test in which a list of 12 words from three taxonomic categories is presented and the respondent is asked to recall as many as possible after each of three learning trials
Visual learning	*Brief Visuospatial Memory Test—Revised* (BVMT-R™)	A test that involves reproducing six geometric figures from memory
Reasoning and problem solving	*Neuropsychological Assessment Battery*® (NAB®): Mazes	Seven timed paper-and-pencil mazes of increasing difficulty that measure foresight and planning
Social cognition	*Mayer-Salovey-Caruso Emotional Intelligence Test* (MSCEIT™): Managing Emotions	Paper-and-pencil multiple-choice test that assesses how people manage their emotions

Table 2. Original neuroendocrine and supplemental biomarkers integrated into the biological assessment

A. **Neuroendocrine markers proposed in the original grant** (all, Yehuda Lab—JJP VAMC)

24- hour urinary Cortisol and Norepinephrine (NE)
Diurnal variation in salivary Cortisol (x7)
Dexamethasone (dex) suppression (low-dose) test including
  Pre-and post-dex Cortisol
  Pre-and post-dex ACTH
  Post-dex Dex level
Plasma NPY
Plasma Cortisol/DHEA; Cortisol/DHEAS
Lysozyme IC-50dex / Glucocorticoid receptor binding

B. **Supplemental biomarkers added with "Plus-up" funding:**

Genetic: Genotyping (Yehuda/ Buxbaum lab, MSSM)
Gene expression (Yehuda/ Buxbaum lab, MSSM; Marti Jett, Walter Reed)

Epigenetic Methylation (Yehuda/ Buxbaum lab, MSSM)
Histone acetylation (Yehuda/ S. Akbarian, MSSM)

Cellular DNA telomere length / telomerase activity (L. Blackburn, UCSF)
Metabolomics / Proteomics (M. Jett, Walter Reed; L. Hood, U Washington)[1]

Cellular metabolic activity:
F2-isoprostanes (Jason Morrow, UCSF)
Oxidative stress (O. Wolkowitz, S. Mellon, UCSF)
Antioxidants (vitamin C) (O. Wolkowitz, S. Mellon, UCSF)
Glutathione peroxidase (Kronos Lab, UCSF)

Immune indices: Cytokines (IL-6, IL-10 and TNG-alpha) (F. Dhahbar, UCSF)

Cardiometabolic indices related to stress:
High sensitivity C-reactive protein (hs-CRP)
Lipid panel, blood pressure, anthropometrics (BMI)

Steroid indices: Glucocorticoid metabolites (F, E, αTHF, βTHF, THE) (Yehuda lab, JJP VAMC)
Derived indices of glucocorticoid metabolic enzyme activities

Neurochemicals: Plasma BDNF (Yehuda, JJP VAMC; Wolkowitz, UCSF)
Plasma endocannabinoids (M. Hill, U. Calvary, Canada)

[1] In discussion with our Program Officer, Dr. Hoover, we will add or delete measures to keep pace with biomarkers identified in the 'Biomarkers in PTSD' study (as well as other efforts), and as new technologies become available.

Table 3. Summary of participant flow to date.

Summary of Participant Flow
20 signed consent
3 dropped out after consent (001, 004, 007)
3 awaiting psych/med evaluations (018, 019, 020)
14 completed both medical and psychological evaluations
1 ineligible due to medical exclusion (006 diabetes)
1 ineligible due to psychological exclusions (009 CAPS of 51 only)
12 included
1 on hold to do pre-tx biology (012 waiting for specific therapist)
11 completed pre-tx biology
11 randomized
11 started PE
1 dropped out after PE session #5 (011)
1 dropped out after PE session #1 (016)
4 currently in treatment (013, 014, 015, 017)
5 completed PE
5 completed post-evaluations
5 completed follow up evaluations (002, 003, 005, 008, 010)

Table 4. Research procedures completed to date

A. Psychological Evaluations			
	Pre-tx	**Post-tx**	**Follow-Up**
Pre-inclusion medical eval	14	--	--
Clinician-rated psychological eval	14	5	5
Self-reports	14	5	5
Cognitive testing	11 of 12	5	5

B. Biological Evaluations / Procedures			
	Pre-tx	**Post-tx**	**Follow-Up**
24-hr urine	11	5	5
Salivary cortisol	--	--	--
Cortisol (7 samples/procedure)	11	5	5
Pre-session cortisol (#8/subject)	56		--
DST Day 1	12	5	5
DST Day 2	11	5	5

C. Biological Assays (run to date)			
	Pre-tx	**Post-tx**	**Follow-Up**
24-hr Urine	**11**	**5**	**5**
cortisol	10	5	4
creatinine	10	4	4
metabolites	0	0	0
Salivary cortisol	--	--	--
Cortisol (7 samples/procedure)	10 of 10	5 of 5	4 of 5
Pre-session cortisol (#8/subject)	45 of 56		--
DST Day 1	**12**	**5**	**5**
cortisol	12	5	4
ACTH	12	5	4
DHEA	12	5	5
DHEAS	12	4	5
NPY	12	5	4
Lysozyme IC50	12	5	4
GR binding	0	0	0
DST Day 2	**11**	**5**	**4**
cortisol	11	5	4
ACTH	11	5	5
dex level	7	5	2

Table 5. Psychological and neuroendocrine descriptive data to date (i.e., Hcort and placebo recipients)

Measure	Pre-treatment (n=12)	Post-treatment (n=5)	Follow-up (n=5)
A. Psychological measures			
Clinician Administered PTSD Scale – total score	84.8 ± 15.9	61.8 ± 23.8	58.6 ± 36.4
CAPS – Intrusive subscale	23.1 ± 6.1	16.0 ± 7.5	16.6 ± 13.4
CAPS – Avoidance subscale	31.8 ± 7.9	21.2 ± 9.9	16.6 ± 14.7
CAPS – Hyperarousal subscale	29.9 ± 4.4	24.8 ± 11.3	25.4 ± 9.5
Montgomery-Äsberg Depression Rating Scale	29.9 ± 5.4	24.2 ± 4.9	22.4 ± 12.7
PTSD Symptom Scale (self-report) – total score	31.2 ± 8.9	27.4 ± 12.4	25.6 ± 14.9
PSS-SR – Intrusive subscale	10.3 ± 2.9	7.0 ± 3.7	8.2 ± 4.8
PSS-SR – Avoidance subscale	15.1 ± 4.1	10.2 ± 5.1	9.0 ± 6.4
PSS-SR – Hyperarousal subscale	11.8 ± 2.9	10.2 ± 4.3	8.4 ± 4.2
Beck Depression Inventory– total score	24.4 ± 5.9	22.8 ± 12.5	22.8 ± 11.3
State-Trait Anxiety Inventory – total score	77.6 ± 14.9	71.0 ± 16.5	78.2 ± 16.3
State-Trait Anxiety Inventory – State	36.7 ± 9.1	35.2 ± 9.8	40.6 ± 10.5
State-Trait Anxiety Inventory – Trait	40.6 ± 10.5	35.8 ± 7.7	37.6 ± 6.3
Posttraumatic Cognitions Inventory – total	129.2 ± 28.8	123.8 ± 52.0	116.2 ± 45.7
PTCI – Negative Self subscale	3.8 ± .9	3.9 ± 1.3	3.4 ± 1.6
PTCI – Negative World subscale	5.4 ± .9	5.2 ± 1.3	4.6 ± 1.7
PTCI – Self Blame subscale	2.5 ± 1.3	3.0 ± .3	2.7 ± 1.2
B. Neuroendocrine data	**Pre-treatment (n=12)**	**Post-treatment (n=5)**	**Follow-up (n=5)**
24hr urinary cortisol (µg/24h)	55.1 ± 27.7	35.9 ± 17.6	58.0 ± 37.5
Urinary creatinine (g/24h)	2.28 ± .85	1.78 ± 1.04	2.83 ±1.27
Lymphocyte lysozyme $IC_{50\text{-}DEX}$ (nMdex)	4.7 ± 2.8	4.2 ± 2.0	4.1 ± 1.4
Plasma NPY (pmol/L)	86.6 ± 37.8	88.9 ± 43.6	59.7 ± 41.5
Plasma DHEA (ng/mL)	9.5 ± 5.5	8.6 ± 3.6	13.3 ± 8.4
Plasma DHEA-S (µg/dL)	226.4 ± 111.1	225.1 ± 244.7	291.3 ± 157.0
Cortisol/DHEA	2.07 ± .86	1.59 ± .25	1.49 ± .59
Cortisol/DHEA-S	.102 ± .084	.089 ± .047	.069 ± .043
Pre-Dex cortisol (µg/dL)	16.4 ± 3.8	13.4 ± 5.0	13.9 ± 6.4
Post-Dex cortisol (µg/dL)	4.1 ± 2.9	5.9 ± 6.7	4.6 ± 5.2
Percent suppression cortisol	75.4 ± 16.3	60.2 ± 41.2	73.2 ± 18.0
Pre to Post-Dex delta cortisol (µg/dL)	11.9 ± 3.2	7.5 ± 6.1	9.3 ± 1.7
Dexamethasone level (ng/dL)	147.2 ± 102.6	115.1 ± 80.1	154.2 ± 2.1
Pre-Dex ACTH (pg/mL)	47.5 ± 22.8	39.1 ±18.3	62.5 ± 45.9
Post-Dex ACTH (pg/mL)	18.1 ± 15.3	19.9 ± 17.9	32.2 ± 21.2
Percent suppression ACTH	67.2 ± 13.9	57.2 ± 36.6	47.9 ± 29.0
Pre to Post-Dex delta ACTH	31.1 ± 10.1	19.2 ± 10.6	30.9 ± 26.5
Salivary cortisol, maximum (ng/mL)	933.4 ± 309.2	4815.8 ± 8802.9	919.4 ± 211.2
Salivary cortisol, minimum (ng/mL)	158.7 ± 57.2	764.0 ± 1206.0	137.8 ± 90.0
Salivary cortisol, mean (ng/mL)	470.7 ± 116.9	2048.3 ± 3460.5	484.1 ± 83.5
Salivary cortisol, max to mean	1.96 ± .28	1.88 ± .49	1.90 ± .38